

We claim:

1. A method executed by a computer under the control of a
program, said computer including a memory for storing said program, said
5 method comprising the steps of:

receiving at least one protein backbone structure;

10 applying a protein design algorithm to generate a protein sequence
and structure;

sampling and evaluating one or more amino acids and rotamers
within the context of said protein sequence and structure;

15 generating a probability matrix for said amino acids and rotamers
that represent the viable sequence space for said protein
backbone.

2. A method according to claim 1 further comprising the step of:

20 generating a single protein sequence from said probability
matrix.

3. A method according to claim 1 further comprising the step of:

25 generating a combinatorial library of proteins from said
probability matrix.

4. A method according to claim 1 wherein said steps are repeated
30 more than once to generate said probability matrix

5. A method according to claim 1 wherein said protein design algorithm comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

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6. A method according to claim 1 wherein said protein backbone structure is taken from a natural protein.

7. A method according to claim 1 wherein said protein structure is generated by comparative modeling.

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8. A method according to claim 1 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

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9. A method according to claim 1 wherein said protein backbone structure comprises an ensemble of related protein backbone structures.

10. A method according to claim 9 further comprising the step of:

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generating a single protein sequence from said probability matrix.

11. A method according to claim 9 further comprising the step of:

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generating a combinatorial library of proteins from said probability matrix

12. A method according to claim 9 wherein said steps are repeated more than once to generate said probability matrix.

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13. A method according to claim 9 wherein said protein design algorithm comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

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14 A method according to claim 9 wherein said ensemble of related protein backbone structures are taken from a family of natural proteins.

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15. A method according to claim 9 wherein said ensemble of related backbone structures is derived from an NMR structure.

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16. A method according to claim 9 wherein said ensemble of related protein backbone structures is generated by a Monte Carlo simulation.

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17. A method according to claim 9 wherein said ensemble of related protein backbone structures is generated by a molecular dynamics simulation.

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18. A method according to claim 9 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

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19. A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

receiving at least one complete protein sequence and structure;

sampling and evaluating one or more amino acids and rotamers

27. A method according to claim 19 wherein said protein sequence and structure is generated by comparative modeling.

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28. A method according to claim 19 wherein said protein sequence and structure is taken from a natural protein.

29. A method according to claim 19 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

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30. A method for optimizing simulation or scoring function parameters that utilizes comparisons between designed sequences and natural sequences, comprising the steps of:

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designing a protein sequence;

comparing said designed protein sequence to natural protein statistics;

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modifying said simulation or scoring function parameters consistent with said comparison.

31. A method according to claim 30 wherein said steps are repeated at least once.

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32. A method according to claim 30 wherein said natural protein statistics are in the form of a position specific scoring matrix.

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33. A method according to claim 30 wherein said natural protein

